Sleep Medicine ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Effect of below-the-knee compression stockings on severity of obstructive sleep apnea

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ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form 5 November 2014
Accepted 7 December 2014
Available online

Keywords:
Obstructive sleep apnea
Fluid shifts
Compression stockings
Upper airway

ABSTRACT

Background: Overnight fluid shift from the legs to the neck may narrow the upper airway and contribute to obstructive sleep apnea (OSA) pathogenesis. We hypothesized that below-the-knee compression stockings will decrease OSA severity in a general OSA population by decreasing daytime leg fluid accumulation and overnight fluid shift and increasing upper-airway size.
Methods: Patients with OSA (apnea–hypopnea index ≥10) were randomized to wear compression stockings during the daytime or to a control group for 2 weeks. Overnight polysomnography with measurement of leg and neck fluid volumes and upper-airway cross-sectional area before and after sleep was performed at baseline and follow-up. The primary outcome was change in the apnea–hypopnea index.
Results: Twenty-two patients randomized to compression stockings and 23 to control completed the study. The apnea–hypopnea index decreased significantly more in the compression stockings than in the control group (from 32.4 ± 20.0 to 23.8 ± 15.5 vs. from 31.2 ± 25.0 to 30.3 ± 23.8, $p = 0.042$), in association with a significantly greater reduction in the overnight decrease in leg fluid volume ($p = 0.028$), and a significantly greater increase in morning upper-airway cross-sectional area ($p = 0.006$). Overnight change in neck fluid volume was unchanged.
Conclusion: These observations suggest that in, a general OSA population, below-the-knee compression stockings decrease OSA severity modestly via attenuation of overnight fluid shift and consequent upper-airway dilatation.

1. Introduction

Obstructive sleep apnea (OSA) is a common condition caused by repetitive collapse of the upper airway during sleep. Continuous positive airway pressure (CPAP), the most common treatment for OSA, is effective but poorly tolerated by many patients. Therefore, new treatments are needed [1]. One novel therapeutic target may be fluid accumulation in the neck during sleep, which may narrow the upper airway and increase its collapsibility [2]. During the daytime, fluid collects in the intravascular and interstitial spaces of the legs due to gravity, and at it night redistributes rostrally towards the neck where it may increase peripharyngeal tissue pressure and narrow the upper airway [3]. Daytime leg fluid accumulation is exacerbated by sedentary lifestyle and prolonged sitting [4]. In nonobese men, the frequency of apneas and hypopneas per hour of sleep (apnea–hypopnea index, AHI) correlated with the volume of fluid moving out of the legs overnight, which was in turn related to the degree of overnight increase in neck circumference as well as the time spent sitting during the daytime [3].

Compression stockings, a widely used treatment for varicose veins and edema, exert pressure on the legs and reduce dependent fluid movement from the intravascular to the interstitial space by counteracting the capillary hydrostatic pressure [5]. In two small studies involving sedentary men and in patients with chronic venous insufficiency, thigh-length compression stockings reduced the AHI by approximately 35% in association with reductions in the volume of fluid moving out of the legs overnight [6,7].

Abbreviations: AHI, Apnea–hypopnea index; CPAP, Continuous positive airway pressure; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire-10; LFV, Leg fluid volume; NFV, Neck fluid volume; NSAID, Nonsteroidal anti-inflammatory drug; OSA, Obstructive sleep apnea; PVT, Psychomotor vigilance task; REM, Rapid eye movement; UA-XSA, Upper airway cross-sectional area.

Clinical trial registration: www.controlled-trials.com (ISRCTN39411395).

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http://dx.doi.org/10.1016/j.sleep.2014.12.005
1389-9457/

However, no randomized studies of compression stockings in unselected OSA patients have been reported. Furthermore, thigh-length stockings are impractical to wear for individuals without varicose veins or edema and are unlikely to be tolerated well by the general OSA population. By contrast, below-the-knee compression stockings are much easier to apply and should be better tolerated in this population. Therefore, we performed a randomized controlled trial to test the hypothesis that, in a general OSA population, below-the-knee compression stockings will reduce the AHI in association with a reduction in overnight leg fluid volume (LFV) change. We further hypothesized that the reduction in overnight LFV change with compression stockings would be associated with a reduction in the overnight increase in neck fluid volume (NFV) and an increase in upper-airway cross-sectional area (UA-XSA).

2. Methods

2.1. Subjects

The inclusion criteria were patients aged 18–80 years referred to the University Health Network Toronto General Hospital Sleep Clinic for polysomnography because of a clinical suspicion of and diagnosed with OSA (AHI ≥10 with ≥50% of events obstructive). The exclusion criteria were OSA treated within the last 3 months, total sleep time <1.5 h, current use of compression stockings, tonsillar hypertrophy, history of heart failure, stroke or end-stage renal or liver disease, and use of drugs affecting fluid balance or level of consciousness (eg, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, sedatives, and opiates) at any time during the study. The protocol was approved by the Research Ethics Board of the University Health Network, and all patients provided written informed consent before participation.

2.2. Polysomnography

Overnight polysomnography was performed using standard techniques and scoring criteria for sleep stages and arousals [8]. Thoracoabdominal motion was monitored by respiratory inductance plethysmography and nasal airflow by nasal pressure cannulae. Oxyhemoglobin saturation (SaO_2) was monitored by oximetry. Apneas were defined as ≥90% reduction in airflow or thoracoabdominal motion from baseline, respectively, lasting ≥10 s. Hypopneas were defined as ≥30% reduction airflow lasting ≥10 s, associated with a ≥3% desaturation or an arousal from sleep [9]. They were classified as obstructive if there was out-of-phase thoracoabdominal motion or flow limitation on the nasal pressure tracing, and central if there was absent thoracoabdominal motion, or in-phase thoracoabdominal motion without evidence of airflow limitation, during apneas and hypopneas, respectively. Signals were recorded on a computerized sleep recording system and scored by technicians blind to the randomization of the patient and to measurement of NFV and LFV. The AHI and the frequency of oxygen desaturations of ≥3% per hour of sleep (oxygen desaturation index, ODI) were quantified.

2.3. NFV and LFV and neck and calf circumferences

Weight was measured before going to bed and within 30 min of awakening the next morning before urinating. Leg edema was assessed before sleep on a scale of 0–3 [10]. With subjects instrumented for sleep studies, lying awake and supine, LFV and NFV were measured simultaneously using a bioelectrical impedance spectrum analyzer (MP150, Biopac Systems Canada, Inc., Montreal, Canada). This well-validated technique uses impedance to electrical current within a body segment to measure the fluid content [11]. For NFV, electrodes were placed behind the right ear and at the base of the right side of the neck. For LFV, electrodes were placed on the ankle and upper thigh of both legs in order to capture reductions in LFV due to both edema reduction in the lower leg and increased venous return throughout the whole leg following the use of compression stockings. Electrodes were secured in place with adhesive tape and the distance between them measured to ensure they were placed the same distance apart at baseline and follow-up. Neck circumference and calf circumferences were measured as previously described [3]. Measurements of LFV, NFV, and neck and calf circumferences were repeated the next morning after awakening before subjects got out of bed and the overnight changes calculated. Measurements were made before the polysomnograms were scored such that the experimenter was blind to the AHI.

2.4. Upper-airway cross-sectional area

Intraluminal UA-XSA before and after sleep was measured by acoustic pharyngometry (Eccovision, Hood Laboratories, Pembroke, MA, USA), with the patient lying supine and the head in the neutral position as previously described [12,13].

2.5. Assessment of sleepiness, sitting time, and physical fitness

Before polysomnography, patients completed the Epworth Sleepiness Scale (ESS) and the short form of the Functional Outcomes of Sleep Questionnaire (FOSQ-10) [13–15]. They performed the psychomotor vigilance task (PVT; PVT-192, CWE Inc., Ardmore, PA, USA), a validated test of alertness that involves reacting as quickly as possible to the appearance of a light by pressing a button on a handheld device [16]. Results obtained included the mean reaction time and the number of false reactions (response to no signal) and lapses (reaction time >500 ms). Patients completed a diary of the number of hours spent sitting during that day and, at baseline, the Duke Activity Status Index, a measure of physical fitness [17].

2.6. Compression stockings

Patients were fitted with appropriately sized, off-the-shelf, below-the-knee compression stockings that apply a pressure of 20–30 mmHg at the ankle. Patients were instructed to wear them every day, commencing the morning after the baseline polysomnogram, putting them on immediately after awakening and removing them just before getting into bed. Patients completed a daily diary of the times the stockings were worn.

2.7. Study design

This was a 2-week randomized controlled trial. Prior to the baseline polysomnogram, patients were randomized according to a computer-generated random schedule in permuted blocks of two and four to either wear compression stockings during the study period or to a control group, with no intervention. Measurements were taken at baseline and at the end of the 2-week study period. Patients received a telephone call after 1 week to enquire about any changes in their health or medications and, for the compression stockings group, to determine that the stockings continued to fit well and to check for any side effects. No patients were treated for OSA by CPAP or any other intervention during the study period.

2.8. Outcome measures

The primary outcome was the change in AHI from baseline to follow-up. Secondary outcomes were changes in ODI, fluid volumes, UA-XSA, ESS, FOSQ-10, PVT results, and sleep structure.

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2.9. Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as proportions. Results were analyzed on an intention-to-treat basis irrespective of compression stockings usage. Baseline data were compared between groups using unpaired *t*-tests, Mann–Whitney *U* tests, or chi-squared tests. Changes from baseline to follow-up within each group were analyzed using paired *t*-tests or Wilcoxon tests. Repeated measures analysis of variance was used to assess changes in variables from baseline to follow-up between groups. A *p*-value of <0.05 was considered significant. A sample size was calculated assuming a 35% reduction in AHI based on a previous randomized trial [7], a two-tailed α of 0.05 and β of 80%. The resulting sample size was 19 patients per group. Taking into account an estimated attrition of four patients per group, the sample size calculated was 46. Statistical analyses were performed by SPSS 20 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients

Study participant flow is shown in Fig. 1. Fifty-seven patients were enrolled and randomized between July 2012 and December 2013 of whom 45 completed the protocol. Patients were randomized just before starting the protocol so that patients in the intervention group could start wearing compression stockings immediately after the baseline polysomnogram. However, because randomization occurred before the baseline polysomnogram results were available, eight patients (five in the compression stockings group and three in the control group) were randomized who did not subsequently meet the inclusion criteria because their AHI was <10 ($n = 7$) or they slept <1.5 h ($n = 1$) on the baseline polysomnogram. Therefore, these patients did not continue with the protocol. Additionally, in the compression stockings group, one patient met the exclusion criteria during the study period due to the use of NSAIDS. Baseline characteristics, shown in Table 1, were comparable between the two groups. Participants were typical of the OSA population in that they were predominantly male, middle-aged, and obese. Patients generally had no or minimal edema. Compression stockings were worn for 14.0 ± 1.4 h/day for 13.9 ± 0.9 days. They were well tolerated and there were no adverse events related to their use.

3.2. Fluid volume changes and UA-XSA

At baseline, in both groups, there were similar overnight reductions in LFV and calf circumference, accompanied by similar overnight increases in NFV and neck circumference (Table 2). At follow-up, the compression stockings group experienced significantly greater reductions in the evening calf circumference (–0.5 ± 0.5 vs. 0 ± 0.5 cm, $p < 0.001$) and leg edema ($p = 0.05$) than the control group. However, there was no significant difference in the change in the evening LFV between groups. At follow-up, the compression stockings group also experienced greater reductions in the overnight decrease in LFV (–90 ± 167 vs. 39 ± 202 ml, $p = 0.03$, Table 2), with a corresponding greater reduction in the overnight decrease in calf circumference (–0.4 ± 0.3 vs. 0 ± 0.5 cm, $p = 0.001$, Table 2) than the control group. However, at follow-up, there were no significant differences between the two groups in the overnight changes in NFV and neck circumference. Although from baseline to follow-up there was no significant difference in evening UA-XSA between the two groups, morning UA-XSA increased significantly more in the compression stockings group than in the control group (0.22 ± 0.46 vs. –0.18 ± 0.39 cm^2, $p = 0.006$, Table 2).

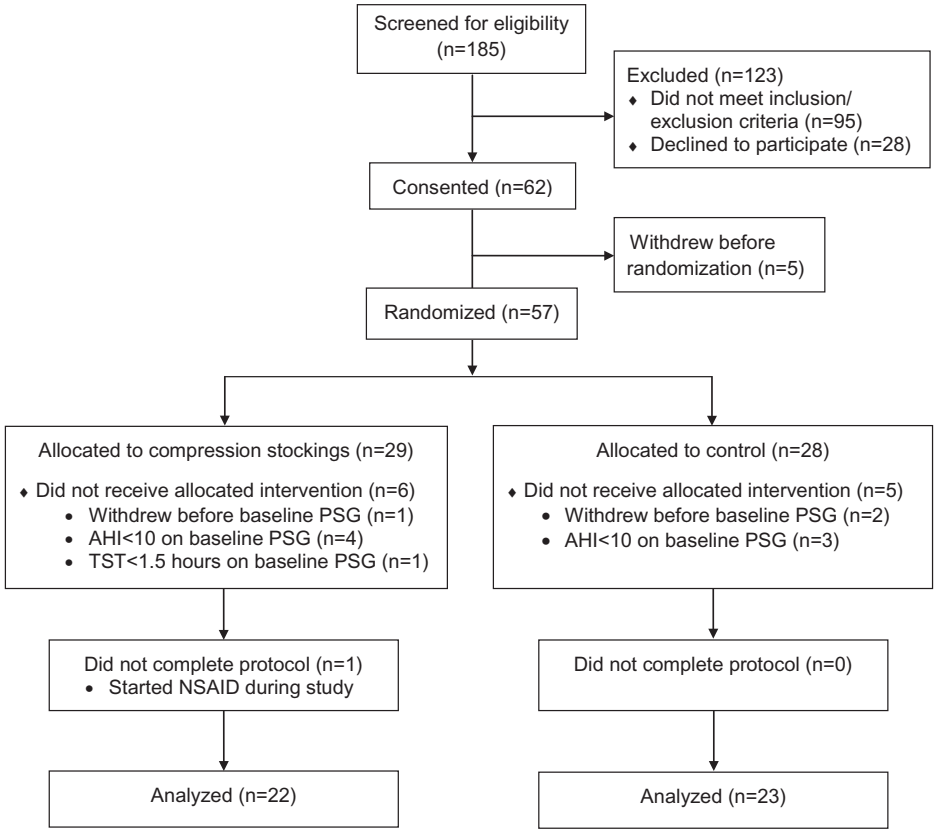

Fig. 1. Study participant flow. AHI = apnea–hypopnea index; PSG = polysomnogram; NSAID = nonsteroidal anti-inflammatory drug; TST = total sleep time.

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Table 1
Baseline characteristics.

	Compression stockings ($n = 22$)	Control ($n = 23$)	p
Age (years)	57.7 ± 11.2	58.0 ± 10.4	0.92
Male sex, n (%)	13 (59.1)	14 (60.9)	0.90
Weight (kg)	91.4 ± 22.5	91.9 ± 18.3	0.75
BMI, kg/m^2	30.7 ± 6.0	31.9 ± 6.6	0.54
Neck circumference (cm)	42.8 ± 5.3	44.2 ± 4.5	0.33
Hypertension, n (%)	14 (63.6)	11 (47.8)	0.29
Ischemic heart disease, n (%)	2 (9.1)	3 (13.0)	0.67
Atrial fibrillation, n (%)	2 (9.1)	5 (21.7)	0.24
Diabetes, n (%)	1 (4.5)	1 (4.3)	0.97
Antihypertensive medications, n (%)	9 (40.9)	11 (47.8)	0.64
ACE inhibitor	1 (4.5)	5 (21.7)	0.09
Angiotensin receptor blocker	6 (27.3)	4 (17.4)	0.43
Beta-blocker	5 (22.7)	4 (17.4)	0.66
Calcium channel blocker	3 (13.6)	5 (21.7)	0.48
Edema score	0.6 (0.5–1.0)	0.5 (0–1.0)	0.47
Duke Activity Status Index	50.5 (38.2–58.2)	46.2 (32.2–58.2)	0.57
Sitting time (h/day)	9.3 ± 3.1	9.2 ± 2.5	0.99
Epworth Sleepiness Scale score	9.8 ± 3.9	6.2 ± 2.9	0.00
AHI (events/h)	32.4 ± 4.3	31.2 ± 5.2	0.86
Obstructive AHI (events/h)	31.3 ± 19.9	28.2 ± 20.7	0.42
Central AHI (events/h)	1.0 ± 2.0	2.2 ± 5.3	0.25
Non-REM AHI (events/h)	29.6 ± 21.9	28.8 ± 26.7	0.64
REM AHI (events/h)	41.7 ± 23.1	39.2 ± 22.5	0.72

Data expressed as mean ± standard deviation or median (interquartile range) unless stated otherwise. ACE, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; BMI, body mass index; REM, rapid eye movement.

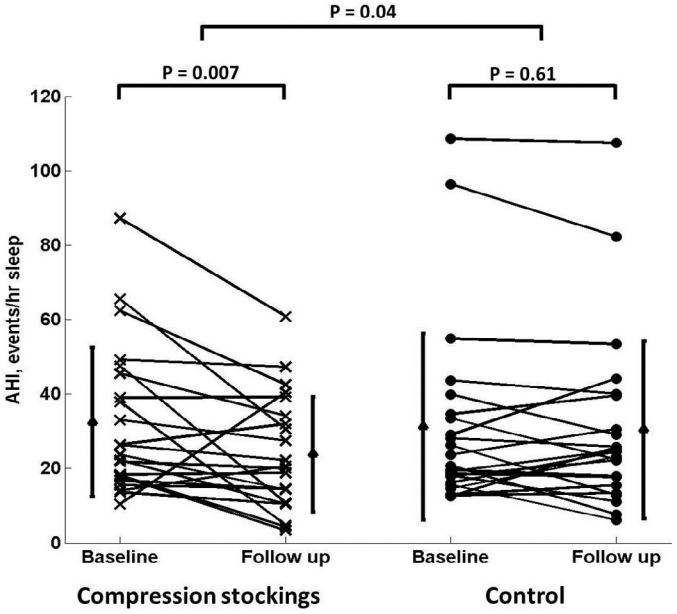

Fig. 2. Changes from baseline to follow-up in the apnea–hypopnea index (AHI) in the compression stockings and control groups. There was a significantly greater reduction in the AHI in the compression stockings group than in the control group.

3.3. Apnea–hypopnea index

At follow-up, the compression stockings group experienced a significantly greater decrease in the AHI than the control group (–8.6 ± 15.3 vs. –0.9 ± 8.5, $p = 0.04$, Fig. 2). This represented a 27% reduction in AHI in the compression stockings group (from 32.4 ± 20.0 to 23.8 ± 15.5, $p = 0.007$), in contrast to the control group in which there was no significant change (from 31.2 ± 25.0 to 30.3 ± 23.8, $p = 0.61$). There was no significant change in central AHI from baseline to follow-up in the compression stockings ($p = 0.93$) or control group ($p = 0.28$), nor were there significant between-group differences (0 ± 2.8 vs. –1.0 ± 3.6, $p = 0.51$). When the AHI was divided into non-rapid eye movement (REM) and REM components, there was a significant reduction in the non-REM AHI within the compression stockings group ($p = 0.04$), but not in the control group ($p = 0.50$). However, the between-group difference in the reduction in the non-REM AHI was of borderline significance (–8.2 ± 16.0 vs. –1.0 ± 9.2, $p = 0.07$). There were no significant differences in the change in REM AHI from baseline to follow-up in either group, nor was the between-group difference significant (–8.0 ± 23.5 vs. 4.1 ± 26.6, $p = 0.12$). At follow-up, the ODI decreased significantly more in the compression stockings group than the control group ($p = 0.03$, Table 3).

In an attempt to identify factors associated with greater AHI reductions with compression stockings, in a post hoc analysis, patients in the compression stockings group were divided into two groups by the median AHI change (a reduction of 4.8), indicating a >4.8

Table 2
Changes in fluid volumes and upper-airway cross-sectional area.

	Compression stockings		Control		p[c]
	Baseline	Follow-up	Baseline	Follow-up	
Body weight (kg)	91.4 ± 22.5	91.2 ± 22.5	91.9 ± 18.3	92.0 ± 18.1	0.49
Overnight change in weight (kg)	–0.7 ± 0.4	–0.8 ± 0.4	–0.9 ± 0.5	–0.7 ± 0.4[a]	0.04
Edema score	0.6 (0–1.0)	0.5 (0–0.5)[a]	0.5 (0–1.0)	0.5 (0–1.0)	0.05
Evening calf circumference (cm)[d]	40.1 ± 3.2	39.7 ± 3.4[b]	40.3 ± 3.9	40.4 ± 3.8	0.00
Morning calf circumference (cm)[d]	39.2 ± 3.3	39.1 ± 3.4	39.3 ± 3.6	39.3 ± 3.7	0.20
Overnight change in calf circumference (cm)[d]	–1.0 ± 0.4	–0.6 ± 0.4[b]	–1.2 ± 0.5	–1.1 ± 0.4	0.00
Evening LFV (ml)	5382 ± 1353	5265 ± 1355	4955 ± 1002	4987 ± 960	0.26
Morning LFV (ml)	4802 ± 1303	4779 ± 1273	4421 ± 916	4412 ± 842	0.88
Overnight change in LFV (ml)	–575 ± 195	–486 ± 199[a]	–534 ± 193	–574 ± 183	0.03
Evening neck circumference (cm)	42.8 ± 5.3	42.8 ± 5.5	44.2 ± 4.5	43.9 ± 4.7	0.40
Morning neck circumference (cm)	43.1 ± 5.5	43.3 ± 5.6	44.7 ± 4.1	44.4 ± 4.3	0.20
Overnight change in neck circumference (cm)	0.3 ± 1.2	0.5 ± 1.1	0.5 ± 1.1	0.5 ± 1.2	0.86
Evening NFV (ml)	279 ± 85	285 ± 98	253 ± 75	259 ± 83	0.96
Morning NFV (ml)	297 ± 85	297 ± 101	274 ± 73	283 ± 76	0.59
Overnight change in NFV (ml)	19 ± 15	12 ± 38	21 ± 39	24 ± 47	0.45
Evening UA-XSA (cm^2)[e]	2.36 ± 0.39	2.45 ± 0.51	2.42 ± 0.49	2.30 ± 0.66	0.22
Morning UA-XSA (cm^2)[e]	2.37 ± 0.44	2.59 ± 0.62[a]	2.35 ± 0.54	2.17 ± 0.49	0.01
Overnight change in UA-XSA[e]	0.01 ± 0.36	0.14 ± 0.40	–0.07 ± 0.29	–0.13 ± 0.40	0.22

[a] $p < 0.05$ versus baseline value; [b] $p < 0.001$ versus baseline value; [c] p-value comparing change from baseline to follow-up between groups; [d] average of left and right calf circumferences; [e] data unavailable for two and five patients in the compression stockings and control groups, respectively, due to technical problems with measurements. LFV = leg fluid volume; NFV = neck fluid volume; UA-XSA = upper-airway cross-sectional area.

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Table 3
Sleep structure.

	Compression stockings		Control		*p*
	Baseline	Follow-up	Baseline	Follow-up	
Total sleep time (h)	5.77 ± 1.09	5.93 ± 0.96	5.26 ± 0.95	5.26 ± 0.98	0.62
Sleep efficiency (%)	81.4 ± 10.4	86.8 ± 9.8[a]	77.6 ± 10.8	78.3 ± 12.3	0.08
Stage 1 (%)	12.4 ± 9.9	8.7 ± 6.6	10.1 ± 5.8	7.9 ± 4.4	0.46
Stage 2 (%)	56.8 ± 9.9	59.4 ± 13.8	64.1 ± 12.0	67.6 ± 10.4	0.92
Stage 3 (%)	12.9 ± 9.5	13.6 ± 11.0	10.0 ± 7.9	10.6 ± 8.6	0.94
REM (%)	17.9 ± 6.7	18.3 ± 6.7	15.9 ± 7.4	14.0 ± 8.5	0.35
Supine time (h)	1.74 ± 1.25[b]	1.71 ± 1.35	3.09 ± 1.81	2.77 ± 1.71	0.36
Arousal index (events/h of sleep)	20.2 ± 23.3	23.2 ± 23.5	19.2 ± 27.8	18.9 ± 27.7	0.62
Minimum SaO_2 (%)	80.5 ± 10.7	80.5 ± 9.8	81.6 ± 8.0	81.6 ± 8.7	0.88
ODI (events/h)	21.4 (16.6–31.9)	17.5 (10.8–31.2)[c]	17.7 (13.7–47.9)	21.3 (11.0–42.7)	0.03

Data expressed as mean ± standard deviation or median (interquartile range).
ODI = 3% oxygen desaturation index.
[a] $p < 0.005$ versus baseline value.
[b] $p < 0.05$ versus control group baseline value.
[c] $p < 0.05$ versus baseline value.

reduction in AHI or a <4.8 reduction in AHI in response to wearing compression stockings. By definition, there was a significantly greater absolute AHI reduction (–19.8 ± 11.2 vs. 2.6 ± 9.7, $p < 0.001$) and percentage AHI reduction (median (interquartile range) –53.2% (–77.3 to –30.3) vs. –3.8% (–13.7 to 21.2), $p < 0.001$) in the group with greater AHI reduction. There were no differences in age, sex, BMI, neck circumference, edema score, presence of hypertension or cardiovascular disease, baseline fluid volumes, or UA-XSA between the two groups. However, those with the greater AHI reduction had a significantly higher baseline AHI than those with the lesser AHI reduction (41.9 ± 22.4 vs. 22.9 ± 18.4, $p = 0.02$). Patients who had greater reductions in AHI while wearing compression stockings also had a significantly greater reduction in evening LFV from baseline to follow-up ($p = 0.04$) and a tendency towards greater reductions in the overnight decrease in LFV ($p = 0.06$) and the overnight increase in NFV ($p = 0.07$) than in those with lesser reductions in AHI.

3.4. Sleep structure and assessments of sleepiness

At follow-up, there was a significant increase in sleep efficiency in the compression stockings group, but not in the control group. However, the difference in this change between the two groups was not significant (Table 3). There were no other changes in sleep structure. There were no significant differences from baseline to follow-up in ESS, FOSQ-10, or PVT values between the two groups (Table 4).

4. Discussion

Our study has given rise to several novel observations concerning the role of nocturnal fluid redistribution in the pathogenesis and therapy of OSA. First, we demonstrated in a randomized controlled trial that below-the-knee compression stockings induced a significant, albeit modest reduction in the AHI in an unselected OSA population that, unlike previous studies, included obese subjects. Second, we showed that this reduction in AHI was accompanied by a reduction in the amount of fluid shifting out of the legs overnight. Third, reductions in the AHI and overnight fluid shift from the legs were accompanied by an increase in UA-XSA assessed in the morning. Taken together, these findings suggest that a reduction in overnight fluid shift from the legs to the neck with a consequent dilatation of the upper airway was a mechanism involved in the reduction in AHI.

These findings extend those of two earlier studies that tested the effects of thigh-length compression stockings in selected groups of nonobese patients with OSA. In the first, a non-randomized uncontrolled study of six sedentary nonobese men, the use of such thigh-length compression stockings for 1 day was accompanied by a 37% reduction in the AHI in association with a 40% reduction in the amount of fluid shifting out of the legs overnight [6]. In the second, a randomized double crossover trial involving 12 nonobese men and women with chronic venous insufficiency, wearing thigh-length compression stockings for 1 week reduced the AHI by 36% in association with a 60% reduction in the amount of fluid shifting out of the legs overnight compared to a control period [7]. The present study differed from these previous studies in several important ways. First, it included a nontreated control group. Second, the sample size was much larger and included a more broadly representative group of OSA patients comprising both men and women, obese and nonobese individuals, and those without marked edema or venous insufficiency. Third, we used below-the-knee compression stockings that are considerably easier to apply than thigh-length stockings and are likely to be better tolerated. The high usage of the stockings of 14 h/day and the lack of adverse effects in this study confirms that they were well tolerated and safe.

Table 4
Measures of sleepiness.

	Compression stockings		Control		*p*
	Baseline	Follow-up	Baseline	Follow-up	
Epworth Sleepiness Scale	9.8 ± 3.9[a]	10.2 ± 4.6	6.2 ± 2.9	6.2 ± 3.8	0.63
FOSQ-10	15.2 ± 2.9	15.6 ± 2.9	15.7 ± 2.6	15.7 ± 2.8	0.24
Psychomotor vigilance task					
Mean reaction time (ms)	275 ± 49	269 ± 48	273 ± 58	265 ± 38	0.80
False starts	2.2 ± 2.5	2.3 ± 3.2	1.7 ± 2.5	1.8 ± 2.0	0.92
Lapses (reaction time >500 ms)	2.0 ± 3.3	2.2 ± 3.9	2.8 ± 8.2	1.3 ± 2.2	0.65

FOSQ = Functional Outcomes of Sleep Questionnaire.
[a] $p < 0.05$ versus control group baseline value.

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We also assessed UA-XSA and NFV in order to define mechanisms by which compression stockings attenuate OSA. In the compression stockings group, we found that the reduction in overnight fluid shift out of the legs was accompanied by a significant increase in morning UA-XSA. This strongly supports the possibility that an increase in UA-XSA was a mechanism by which compression stockings reduced the AHI. However, although we hypothesized that reducing fluid movement from the legs would increase UA-XSA via a reduction in neck fluid accumulation, the overnight increases in neck circumference and NFV were unchanged from baseline to follow-up in the compression stockings group. By contrast, in two previous studies involving nonobese OSA patients, compression stockings reduced the AHI in association with attenuation of the overnight increase in neck circumference, although NFV was not measured [6,7]. However, it is unknown what degree of NFV change is physiologically significant. In addition, the change in overall NFV may not correlate with change in UA size. For example, there may be a decrease in UA mucosal edema reducing UA size and increasing its collapsibility, which is not detected by measuring overall NFV [18]. There may in fact have been small reductions in NFV that we were unable to detect due to technical factors. Such factors include increased neck adiposity, which may have affected the accuracy of the bioelectrical impedance measurements [19]. Another possibility is that compression stockings reduced thoracic fluid volume, which could have lowered the left ventricular filling pressure and reduced lung water. If so, then reduced stimulation of pulmonary vagal irritant receptors that increase loop gain could have stabilized respiratory control and rendered the upper airway less collapsible [20]. However, as we did not measure thoracic fluid volume, we cannot be certain that this occurred.

Other interventions targeting rostral fluid shift have also attenuated OSA and increased UA-XSA in patients with fluid-retaining conditions who have an increased prevalence of OSA [21,22]. In patients with end-stage renal disease, following conversion from nocturnal to daytime continuous ambulatory peritoneal dialysis, in which there was less fluid removal at night, the AHI increased by 55% in association with a decrease in UA-XSA and an increase in tongue volume [22]. In patients with diastolic heart failure, intravenous diuretics decreased the AHI by 24% in association with an increase in UA-XSA [21]. In an uncontrolled study of hypertensive patients, intensified diuretic therapy for 2 weeks reduced the AHI by 16%, in association with reductions in the overnight fluid shift out of the legs and overnight increase in neck circumference [23].

Although in previous studies we found that the overnight changes in LFV and neck circumference explained approximately 65% of the variability in the AHI, we found that compression stockings only caused a modest 27% reduction in the AHI that was comparable to the effects of other interventions targeting fluid retention as described above [3]. The most likely explanation for this is that compression stockings did not induce a large enough reduction in LFV and overnight LFV shift to eliminate OSA. For example, in the present study, compression stockings decreased the overnight reduction in LFV from 575 to 486 ml. Similarly, aggressive diuretic therapy for drug-resistant hypertensive patients with OSA caused a comparable reduction in the AHI in association with a similar decrease in the overnight reduction in LFV from 418 to 308 ml [23]. These post-intervention overnight LFV reductions remain considerably higher than overnight reductions in LFV of approximately 50 ml in healthy nonobese men without OSA, and approximately 200 ml in heart failure patients without sleep apnea [3,24]. The reason why compression stockings did not reduce overnight fluid shift to within-normal limits is unclear. One possibility is that the pressure applied was not high enough. However, it would be difficult for patients to tolerate pressures >20–30 mmHg chronically. There may also be a ceiling effect regarding how much overnight rostral fluid shift can be prevented, irrespective of the intervention.

Another possible reason why compression stockings and other interventions that target fluid retention and overnight fluid shifts have induced only modest decrements in the AHI is that, in many patients, OSA is liable to be multifactorial in etiology [25]. For example, in some patients, narrowing of the upper airway that facilitates its collapse during sleep is due to anatomical factors such as fat deposition in the peripharyngeal soft tissues or reduced space in the bony envelope due to anomalies such as micrognathia. In others, reduced pharyngeal dilator muscle activity during sleep plays a significant role in inducing upper-airway obstruction during sleep [26]. None of these mechanisms would be affected by interventions targeting fluid shift. Accordingly, the relative contribution of these different factors to the pathogenesis of OSA in an individual patient is likely to influence their response to interventions targeting fluid shifts such as compression stockings. Furthermore, rostral fluid shift may be more important in the pathogenesis of OSA during non-REM than REM sleep, as compression stockings tended to decrease the non-REM but not the REM AHI. This is possibly because, during REM sleep, the main cause of OSA is the profound reduction in upper-airway dilator muscle activity, such that neck fluid accumulation will not have any additional effect on upper-airway collapsibility during REM sleep [27]. This is supported by the finding that rapid intravenous saline infusion during sleep increased the AHI during non-REM, but not REM sleep [28].

In a recent study, it was suggested that rostral fluid shift may not be important in the pathogenesis of OSA as there was no increase in the AHI from the first to the second half of the night, which may occur if there was ongoing fluid accumulation during the night [29]. However, because measurements of fluid volumes were not made, it is difficult to draw conclusions about the role of rostral fluid shift in the pathogenesis of OSA from that study. Moreover, as half the patients had an AHI <5 and therefore did not have OSA, one would not expect an increase in their AHI from the first to the second half of the night.

In the present study, compression stockings reduced OSA severity from the severe to the moderate range. This was accompanied by an improvement in sleep efficiency. However, there were no associated improvements in measures of sleepiness or alertness (ie, ESS, FOSQ-10, or PVT), presumably because there was still significant residual OSA and no reduction in arousal frequency. Consequently, the clinical significance of the 27% reduction in AHI induced by compression stockings remains unclear. Compression stockings might still provide an alternative treatment option for patients intolerant of CPAP, especially those with mild to moderate OSA in whom a 27% reduction in AHI may be more clinically significant than in someone with severe disease. In comparison, oral appliances are a commonly used therapy for OSA despite inducing only modest AHI reductions of 33–56% [30–32]. Another possibility is that, in CPAP-intolerant patients, compression stockings might be used in conjunction with another treatment such as an oral appliance, which is less effective than CPAP in lowering the AHI, but better tolerated [30]. The combination of the two treatments might provide an additive effect, comparable to CPAP, on lowering the AHI. This possibility requires further investigation.

This study is subject to some limitations. The study period was for 2 weeks, and therefore we were not able to determine the long-term effects of compression stockings on OSA severity. Although the inclusion criteria were broad, the results may not apply to, for example, patients taking diuretics or those with fluid-retaining conditions such as heart failure or renal failure. Such patients were excluded because alterations in disease activity, missed medications, or dose adjustments or alterations in dialysis prescription could have affected rostral fluid shift and made it difficult to determine the independent effects of compression stockings on this variable. Finally, patients in the compression stockings group had a higher ESS than those in the control group, suggesting that they were more

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sleepy, although FOSQ-10 scores were similar. However, this is unlikely to have affected the change in AHI or other physiological measures.

In conclusion, this study demonstrated that compression stockings reduced the AHI significantly in a general OSA population with moderate to severe disease. This was accompanied by a significant reduction in the amount of fluid shifting out of the legs overnight and an increase in morning UA-XSA. These data provide further evidence that overnight rostral fluid shift is one factor that contributes to the pathogenesis of OSA in patients without fluid-retaining conditions. Compression stockings could be considered as an alternative or adjunctive therapy in selected patients intolerant of CPAP, but the longer-term efficacy needs to be determined before such a recommendation can be made.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.12.005.

Acknowledgments

This study was supported by a Canadian Institutes of Health Research (CIHR) operating grant MOP-82731. L.H. White was supported by a fellowship from Sleep Country Canada; O.D. Lyons by the Canadian Thoracic Society/European Respiratory Society Peter Macklem Joint Research Fellowship; A. Yadollahi by fellowships from the Toronto Rehabilitation Institute, Mitacs Elevate program, and a CIHR Training Grant in Sleep and Biological Rhythms; and T.D. Bradley by the Clifford Nordal Chair in Sleep Apnea and Rehabilitation Research.

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